Specific support for the amendment to claim 50 can be found in the claims as originally filed including claim 54 (now cancelled). Additional support can be found in Applicants' disclosure particularly at pp. 5-6; 16-21; and 24. See also pp. 20-21, bridging paragraph.

The amendments to claims 52, 55, 57, 59, 61, 62, and 68 are intended to improve claim clarity.

New claim 80 finds particular support at pg. 8, line 20 to pg. 9, line 1 for example.

No new matter has been added by virtue of the claim amendments.

Claims 51, 53, 59, 64, 68 and 70 were objected to on various grounds. The objections have been addressed fully by amendment.

Claims 50-51, and 55-71 stand rejected under 35 USC §112, first paragraph on various grounds. Although Applicants respectfully disagree with the position taken, basis for it has been addressed by amendment.

Specifically, claim 50 has been amended to feature more specific vascularization modulating agents ie., specific hematopoietic factors. Particular disclosure relating to the factors can be found eg., at pg. 20, line 27 to pg. 21, line 13. See also pg. 16, line 15 to pg. 16, line 22 (disclosing various suitable GM-CSF molecules).

Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 50-51 and 54-71 stand rejected under 35 USC §112, first paragraph. Applicants are grateful that the USPTO has found the specification enabling for the method described at pg. 6 of the Office Action. Claim 50, as amended, should also address another of the Examiner's concerns ie., that the specification does not enable use of particular factor fragments. Action at pgs. 9-10, bridging paragraph to pg. 11.

As amended, claim 50 features use of specific hematopoietic factors or fragments of those factors. As the specification makes clear, such molecules are recognized agents for increasing HPC mobilization. See pgs. 20-21 of Applicants' specification. Much is known about the nucleic acid and protein sequence of the featured hematopoietic factors. For instance, pgs. 20-21 provide literature references discussing various CSF factors, SCF, SDF-1, angiopoietin-1, angiopoietin-2, and FLT-3 ligand. See also pg. 21 (referencing the GenBank, EMBL and Swiss-Prot databases for information on these and other factors)

Moreover, the present specification defines an "effective fragment" of a hemopoietic protein as an amino acid sequence that exhibits at least 70% of the vessel promoting activity of the corresponding full-length protein as determined by a standard assay as disclosed by the specification. A preferred assay is one that detects and preferably quantifies EPC mobilization. See pg. 26, lines 2-12. An illustrative assay is the standard hind limb ischemia assay as provided on pg. 24 and the Examples section.

In view of Applicants' detailed disclosure concerning preferred hemopoietic factors for use with the invention, one of skill reading the disclosure would know how to make and use a wide spectrum of fragments. No undue experimentation would be needed to identify and use such fragments.

The USPTO has asserted that one would need to know which amino acids should be substituted, deleted or inserted at which positions of the agents. Action at pg. 12. Respectfully, that is not the case.

Applicant's specification provides several standard assays that can be used to identify and, if needed, determine the activity of the factors without having to know the chemical structure of the fragment. The chemical structure of hematopoietic factors of amended claim 50 have been disclosed both at the amino acid and nucleic acid levels. Important function domains in the structure are already recognized in the field. Methods for producing or obtaining suitable factors from commercial or public sources are also taught. See pg. 21, line 13 to pg. 23, line 5, for example. See also GenBank, EMBL and the Swiss-Prot databases as referenced on pg. 21.

Accordingly, it is believed that any testing needed to identify or confirm effective fragments of the particular hematopoietic factors now recited by amended claim 50 is well within the level of experimentation permitted by the Federal Circuit. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

On pgs. 12-13 of the Action, the position was taken that "relationship between sequence of a peptide and tertiary structure is not well understood and is not predictable". Also, it has been asserted that "the physiological art is recognized as unpredictable". Applicants respectfully disagree with both positions. They are simply not germane to the invention as claimed. To make and use the claimed invention, there is no need to know relationship between the sequence any hematopoietic factor and other structures. The specification provides a variety of standard assays that can be used to help identify full-length or effective fragments of hematopoietic factors. Moreover, use of the invention is certainly not unpredictable in light of Applicants' detailed disclosure about how to make and use the specific and well-known factors in the claimed method.

Claim 54 stands rejected under 35 USC §112, second paragraph. The claim has been cancelled.

Claims 50, 55-65 and 79 stand rejected as being anticipated by the Pu et al. reference. While Applicants disagree with the rejection, basis for it has been addressed. The claimed method does not feature use of FGF. Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 50-51, 55-67, and 79 stand rejected under 35 USC §102(b) as being anticipated by the Franco patent (US Pat. 4,296,100) or Kawakami et al. (Brain Res. 697: 104 (1995). Applicants respectfully disagree with the stated grounds of rejection. However, basis for it has been addressed by amendment. The amended claims do not feature use of FGF. Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 50-51, 55-66, and 79 stand rejected under 35 USC 102(b) as being anticipated by Ferrara et al. (US Pat. 6,133,231). While Applicants disagree, the claims as amended do not feature use of HGF. Reconsideration and withdrawal of the rejection are requested.

Claims 50-53 and 55-79 stand rejected as unpatentable under 35 USC §103 over Hammond et al. (US Pat. No. 5,880,090) in view of Asahara et al. (*Science* 275: 964) or Isner (U.S Pat. No. 5,980,887). Although Applicants respectfully disagree with the rejection, basis for it has been addressed by amendment.

Claim 50 as presently amended includes language from claim 54 (now canceled). Claim 54 was not rejected as obviousness in view of the cited art. Accordingly, the rejection has been rendered moot.

Although it is not believed that any additional fees are needed to consider this submission, the Examiner is hereby authorized to charge our deposit account no. **04-1105** should any fee be deemed necessary.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 51, 53, 54, 64, 69 and 71 have been canceled.

Claims 50, 52, 55, 57, 59, 61, 62, and 68 have been amended as follows.

50. A method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of a [vascularization modulating agent] vascular endothelial growth factor (VEGF) or a hematopoietic factor sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell (EPC) frequency by at least about 20% as determined by a standard EPC isolation assay, wherein the hematopoietic factor is a granulocyte-macrophage colony stimulating factor (GM-CSF), stem cell factor (SCF), stromal cell-derived factor (SDF-1), granulocyte-colony stimulating factor (G-CSF), monocyte-colony stimulating factor (M-CSF), angiopoietin-1, angiopoietin-2, fetal liver tyrosine kinase 3 (FLT-3) ligand, or an effective fragment thereof, and further wherein the method comprises increasing EPC differentiation by at least about 20% as determined by a standard EPC culture assay.

52. The method of claim 50, wherein the [vascularization modulating agent] factor is GM-CSF, and amount of the GM-CSF administered to the mammal is sufficient to increase frequency of endothelial progenitor cells (EPC) in the mammal.

55. The method of claim 50, wherein the amount of [vascularization modulating agent] factor administered to the mammal is sufficient to increase blood vessel length in the mammal.

57. The method of claim 53, wherein the amount of [vascularization modulating agent] factor administered to the mammal is further sufficient to increase blood vessel diameter in the mammal.

59. The method of claim 50, wherein the amount of [vasculanzation modulating agent] factor administered to the mammal is sufficient to increase EPC differentiation following tissue ischemia.

61. The method of claim 50, wherein the amount of administered [vascularization modulating agent] factor is sufficient to increase neovascularization by at least about 5% as determined by a standard cornea micropocket assay.

62. The method of claim 50, wherein the amount of administered [vascularization modulating agent] factor is sufficient to increase EPC incorporation into foci.

68. The method of claim 50, wherein the factor is co-administered with at least one angiogenic protein.

The following new claims 80-81 were added.

80. The method of claim 50 further comprising isolating EPCs from the mammal and administering the EPCs to the mammal.

81. A method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) or a hematopoietic factor sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell (EPC) frequency by at least about 20% as determined by a standard EPC isolation assay, isolating EPCs from the mammal and administering the EPCs to the mammal, wherein the hematopoietic factor is a granulocyte-macrophage colony stimulating factor (GM-CSF), stem cell factor (SCF), stromal cell-derived factor (SDF-1), granulocyte-colony stimulating factor (G-CSF), monocyte-colony stimulating factor (M-CSF), angiopoietin-1, angiopoietin-2, fetal liver tyrosine kinase 3 (FLT-3) ligand, basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF); hepatocyte growth factor (HGF); or an effective fragment thereof, and further wherein the

method comprises increasing EPC differentiation by at least about 20% as determined by a standard EPC culture assay.

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